

# Hereditary breast and ovarian cancer

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Familial breast cancer was first recognized in the Roman medical literature of 100 AD [1]. The first documentation of familial clustering of breast cancer in modern times was published by Broca, who reported 10 cases of breast cancer in 4 generations of his wife's family [2]. In the middle of the nineteen nineties it was proven at the molecular level that a substantial number of breast and ovarian cancers has hereditary monogenic aetiology [3, 4]. Evaluation of frequency of pedigree-clinical signs characteristic for strong aggregations of breast/ovarian cancers among consecutive cases of cancers of these organs as well as analyses of cancer incidence in monozygotic twins indicate that about 30% of breast and ovarian cancers develop because of a strong genetic predisposition [5]. In other breast/ovarian cancers the significance of genetic factors was underestimated. However, recently it has been possible to show the characteristic constitutional background influencing development of cancer also in patients with sporadic neoplasms. Therefore now scientists think that in almost all patients with cancer a certain genetic background should be detectable, although influencing cancer risk to a various degree. Genetic abnormalities strongly related to cancer are called high risk changes (genes) and abnormalities influencing cancer development to a lower degree are called moderate risk changes (genes). Most frequently strong genetic predisposition to breast/ovarian cancers are related to mutations in the *BRCA1* and *BRCA2* genes and most often it appears as syndromes of hereditary breast cancer – site-specific (HBC-ss), hereditary breast-ovarian cancer (HBOC) and hereditary ovarian cancer (HOC).

In family members of families with HBC-ss syndrome only breast cancers but not ovarian cancers are observed. In HBOC syndrome families both breast and ovarian cancers are diagnosed, and in HOC syndrome only ovarian but not breast cancers are detected. Operational clinical-pedigree criteria which we use in

**Table 1.** Pedigree-clinical diagnostic criteria of HBC-ss, HBOC and HOC syndromes [6]

| Number of breast or ovarian cancer cases in family:  |  |
|--|--|
| A – 3 (definitive diagnosis)   |  |
| 1) At least 3 relatives affected with breast or ovarian cancer diagnosed at any age  |  |
| B – 2 (highly probable diagnosis)  |  |
| 1) 2 breast or ovarian cancer cases among first degree relatives (or second degree through male line)                          |  |
| 2) 1 breast cancer and 1 ovarian cancer diagnosed at any age among first degree relatives (or second degree through male line) |  |
| C – 1 (highly probable diagnosis)  |  |
| 1) Breast cancer diagnosed below 40 years of age   |  |
| 2) Bilateral breast cancer   |  |
| 3) Medullary or atypical medullary breast cancer   |  |
| 4) Breast and ovarian cancer in the same person  |  |
| 5) Breast cancer in male   |  |

order to diagnose “definitively” or “with high probability” the discussed syndromes are summarized in Table 1. In the vast majority of cancer cases related to moderate risk genes family history is negative. HBC-ss, HBOC and HOC syndromes are clinically and molecularly heterogeneous. Mutations in the *BRCA1* and *BRCA2* genes are the most frequent cause of these syndromes.

## BRCA1 syndrome

In this syndrome women carry a germline mutation in the *BRCA1* gene. Carriers of a *BRCA1* mutation have approximately 50-80% lifetime risk of breast cancer and 40% risk of ovarian cancer [7]. We estimate that these risks are 66% for breast cancer and 44% for ovarian

**Table 2.** Risk of breast and ovarian cancer in *BRCA1* mutation carriers in Poland [8]

| <b>A. Cumulated risk of breast cancer</b>  |     |     |    |      |      |    |
|--|-----|-----|----|------|------|----|
| Age  | <30 | 40  | 50 | 60   | 70   | 75 |
| Cumulated risk (%)                         | 1.6 | 6.5 | 30 | 40.5 | 50.5 | 66 |
| <b>B. Cumulated risk of ovarian cancer</b> |     |     |    |      |      |    |
| Age  | <30 | 40  | 50 | 60   | 70   | 75 |
| Cumulated risk (%)                         | 1   | 3.5 | 12 | 30   | 41   | 44 |

cancer in the Polish population (Table 2). Both risks appear to be dependent on the type and localization of the mutation [8-10]. Our findings suggest that the risk of breast cancer in women with 5382insC is two times higher than in women with 4153delA.

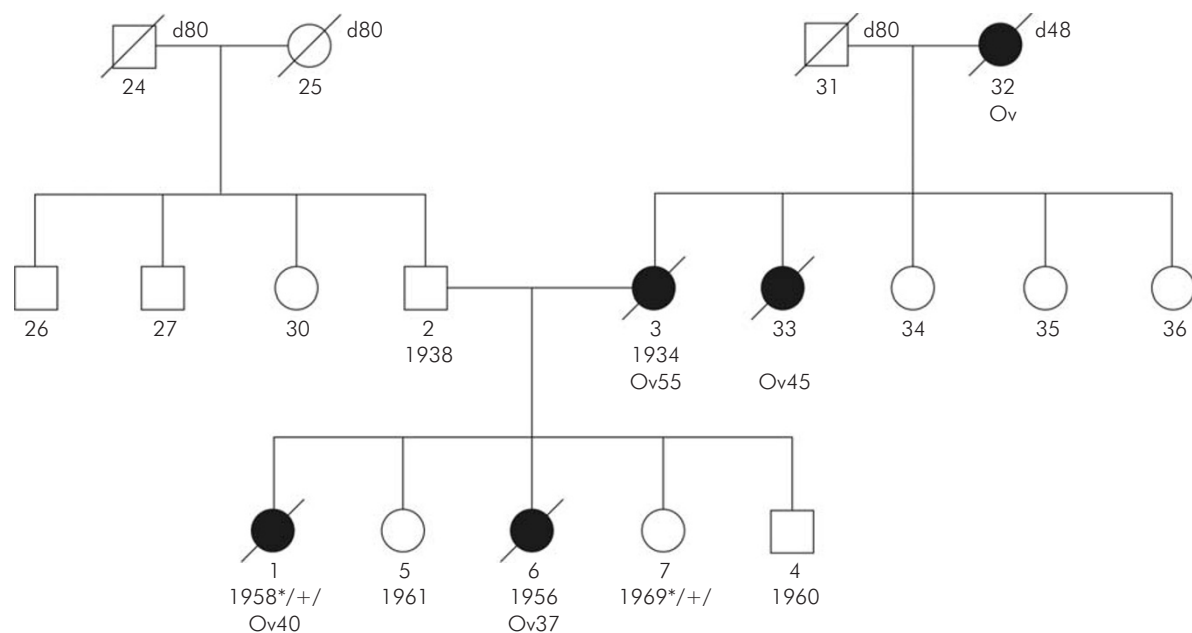
Incomplete penetrance of *BRCA1* suggests that other factors, genetic and non-genetic modifiers, are important in carcinogenesis in the mutation carriers. The risk of ovarian cancer is modified by VNTR locus for *HRAS* 1 and is increased 2-fold in *BRCA1* carriers harbouring one or two rare alleles of *HRAS* 1 [11]. We reported that the 135G>C variant in the *RAD51* gene is strongly protective (OR = 0.5) against both ovarian and breast cancer [12, 13].

Carriers of a *BRCA1* mutation are also at about 10% lifetime risk of fallopian tube and peritoneal cancers [14]. These data about the frequency of ovarian cancer in *BRCA1* carriers appear to reflect the combined frequency of ovarian, fallopian tube and peritoneal cancers, because these tumours were diagnosed as ovarian cancers in the

past, and because they share similar morphology and cause elevated levels of the marker CA 125.

The risk of cancer at other sites may be increased in carriers of a *BRCA1* mutation as well, but the evidence is controversial and needs further studies.

Breast and ovarian cancer in *BRCA1* carriers have particular clinical characteristics. The mean age at onset of breast cancer is about 42-45 years [15, 16] and of ovarian cancer is about 54 years [17, 18]. 18-32% of breast cancers are bilateral [19, 20]. These are rapidly growing tumours: >90% of cases have G3 grade at the time of diagnosis and almost all ovarian cancers in women with a *BRCA1* mutation are diagnosed in FIGO stage III°/IV°. Medullary, atypical medullary, ductal and oestrogen receptor negative (ER) breast tumours are common in *BRCA1* carriers. *BRCA1* mutation-positive tumours constitute about 10-15% of all ER-breast cancers [21-23]. Most carriers of a *BRCA1* mutation report a positive family history of breast or ovarian cancer (Figure 1). However, 45% of *BRCA1*

**Figure 1.** Family with HOC syndrome and diagnosed constitutional 4153delA *BRCA1* gene mutation

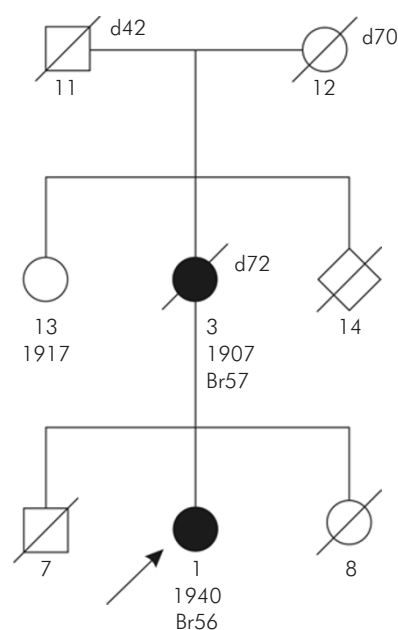
carriers report a negative family history, mainly because of paternal inheritance and incomplete penetrance (Figure 3) [20].

## Molecular diagnosis of constitutional *BRCA1* mutations

This topic has been described in detail in the section “*BRCA1* Test”.

## *BRCA2* syndrome

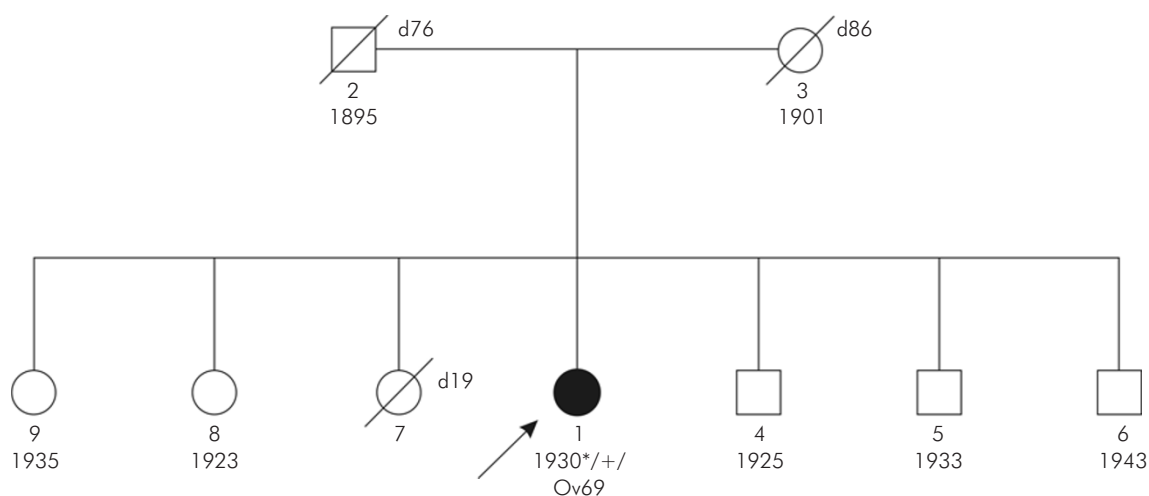
Patients with this syndrome have a constitutional mutation in the *BRCA2* gene [24]. According to literature data lifetime risk for *BRCA2* carriers from families with definitive HBC-ss and HBOC is estimated at 31-56% for breast cancer and 11-27% for ovarian cancer [10, 25-28]. Studies performed in 200 Polish families with strong aggregation of breast and/or ovarian cancers proved that mutations in the *BRCA2* gene are rare, with a frequency of 4%. There are no studies on cumulated cancer risk in *BRCA2* mutation carriers from the Polish population. Most *BRCA2* mutations from the Polish population probably slightly increase breast cancer risk. Studies performed in our centre showed that in families with aggregation of breast cancer diagnosed before the age of 50 and stomach cancer diagnosed in males before the age of 55, frequency of *BRCA2* carriers is about 10-20% [29]. *BRCA2* mutations are also related to a significantly increased although not precisely estimated risk of ovarian cancer and cancers of the digestive tract such as stomach, colon and pancreas in both females and males. Studies performed in our centre showed that



**Figure 2.** Family with fulfilled clinical-pedigree criteria “suspected HBC-ss”. *BRCA1* mutation was not detected

*BRCA2* mutations are detected with a frequency of 30% in families without breast cancer but with aggregation of ovarian cancer with stomach, colon or pancreatic cancer between first and second degree relatives [30]. *BRCA2* studies performed on male breast cancer patients from the Poznań population showed that 15% of patients from this group are mutation carriers [31].

Breast and ovarian cancers in families with *BRCA2* mutations have characteristic features. Medium age of breast cancer is 52 and 53 in females and males, respectively, and 62 for ovarian cancer [31, 32].



**Figure 3.** Patient with ovarian cancer and detected 5382insC *BRCA1* mutation from family with negative family history

## Molecular diagnosis of *BRCA2* mutations *BRCAX* syndrome

Unlike for the *BRCA1* gene, a founder effect for *BRCA2* mutations was not observed with significant frequency in the Polish population [22]. It should be noted that “de novo” mutations are rare in these groups of genes; thus the presence of founder mutations in *BRCA2* is probable. As yet *BRCA2* mutations should be diagnosed individually for each family by full sequencing. Since the *BRCA2* gene is large – about 70 genomic kbp – the cost of sequencing of this gene is high (around 1500 euro).

In families with a detected marker of constitutional mutation the cost of analysis of two independently taken blood samples allowing exclusion or confirmation of carrier status among relatives is low – around 100 euro.

In Poland in about 30% of families with definitively diagnosed HBC-ss and HBOC syndromes and in about 40% of families with HOC syndrome, *BRCA1* or *BRCA2* mutations are not detected. In rare cases it is possible to diagnose one of the rare syndromes listed in Table 3. In these syndromes breast/ovarian cancers are observed with higher frequency. Many groups worldwide are trying to identify new genes causing BRCAX syndrome.

## Clinical management in families with high risk of breast/ovarian cancer

Special management should be applied for:

- carriers of mutations of high breast/ovarian cancer

**Table 3.** Selected rare syndromes with increased risk of breast and/or ovarian cancer

| Disease  | Clinical features   | Gene mutation/<br>Inheritance     | References |
|--|---|-----------------------------------|------------|
| Li-Fraumeni syndrome   | breast cancers, sarcomas, brain tumours, leukaemia, renal gland cancer  | p53, high penetrance, AD          | 17, 33     |
| Cowden disease   | multifocal mucoid skin abnormalities, benign proliferative abnormalities of different organs, thyroid cancers, breast/ovarian cancers | PTEN, AD                          | 34, 35     |
| HNPCC  | colon cancers, endometrial cancers, other organ cancers including breast and ovary  | MSH2, MLH1, AD                    | 36         |
| Peutz-Jeghers syndrome                                       | hyperpigmentation of the mouth, bowel polyps, colorectal cancers, small bowel cancers, gonadal tumours, breast cancers                | STK11, AD                         | 37         |
| Ruvalcaba-Myhre-Smith (Z. Bannayan-Riley-Ruvalcaba) syndrome | macrocephaly, bowel polyps, “café-au-lait” on penis, lymphomas, thyroid cancers, breast cancers                                       | PTEN, AD                          | 38         |
| Heterozygotic carrier status of “ataxia telangiectasia” gene | ocular ataxia, ataxia of cerebellum and skin, hypersensitivity to radiation, different site neoplasm including breast/ovarian cancer  | ATM                               | 39         |
| <i>ATH</i> gene carriers                                     | increased breast cancer risk  | low penetrance 20-40%, AD         | 6          |
| Klinefelter syndrome   | gynaecomastia, cryptorchidism, extragonadal germ cell tumours, male breast cancer   | 47, XXY, low penetrance, <10%     | 40         |
| Androgen receptor gene mutation                              | familial male breast cancer   | androgen receptor                 | 41         |
| Constitutional translocation t(11q;22q)                      | increased breast cancer risk  | balanced translocation t(11q;22q) | 42         |

Inheritance

AD – autosomal dominant, AR – autosomal recessive

risk; usually around 50% of female family members should be included in the programme;

- all family members of families with HBC-ss, HBOC or HOC diagnosed definitively or with high probability according to pedigree criteria shown in Table 1, if constitutional mutations predisposing to cancer were not detected.

Special management concerns:

- prophylactics,
- surveillance,
- treatment.

## Prophylactics

### Oral contraceptives

Contraindications for use of oral contraceptives (OC) by *BRCA1* carriers aged below 25 are well documented. It was shown that OC used for 5 years by young women increase breast cancer risk by about 35% [43]. Since in about 50% of *BRCA1* carriers family history is negative it seems to be necessary to perform the *BRCA1* test in every young woman who wishes to use OC. OC used by *BRCA1* carriers after the age of 30 seems not to influence breast cancer risk [43-45] but shows a 50% reduction of ovarian cancer risk [34], so use of OC after the age of 30 appears to be justified. As yet, there are no verified data concerning the effects of OC in families not related to *BRCA1* mutation. However, there are studies indicating several-fold increased breast cancer risk in OC users from families with breast cancer aggregation [46]; thus it seems reasonable to avoid OC in families with HBC-ss and/or HBOC.

### Hormone replacement therapy (HRT)

Prophylactic oophorectomy at the age of 35-40 is the gold standard for *BRCA1/2* carriers and corresponds with risk reduction for both breast and ovarian cancer. It was shown that carriers after oophorectomy, who use oestrogen HRT, show a similar protective effect as patients who do not use HRT [47, 48]. The influence of HRT in carriers without prophylactic oophorectomy is not well documented. Three-fold increased risk of breast cancer in HRT users with positive breast cancer family history was reported [49]. Therefore, the decision about HRT use should be made with particular caution.

### Breast feeding

Long-term breast feeding is indicated in all females from families with HBC-ss, HBOC and HOC. It was shown in *BRCA1* carriers that breast feeding over 18 months, counting together all pregnancies, reduces breast cancer risk – from 50-80% to 25-40% [50, 51].

## Early delivery

Women from the general population who delivered the first child before the age of 20 are at 50% lower breast cancer risk than nulliparous women. This observation was not confirmed in women with *BRCA1* or *BRCA2* mutation [52]. However, taking into consideration the fact that mutation carriers should elect prophylactic oophorectomy at age 35-40, they should not delay maternity significantly.

## Chemoprevention

### Tamoxifen

Literature data clearly indicate that tamoxifen reduces by about 50% the risk of ER+ breast cancers. This effect was observed in healthy women as well as in women treated for breast cancer, where tamoxifen reduced the risk of contralateral breast cancer. A protective effect of tamoxifen was also observed in *BRCA1* carriers in spite of the fact that most cancers in these patients are ER-. Such an effect of tamoxifen was observed in pre- and postmenopausal women [53, 54]. According to present data it is justified to propose 5 year chemoprevention with tamoxifen to patients from families with HBC-ss, HBOC and *BRCA1* mutation carriers as well after exclusion of all contraindications, especially related to clotting problems and endometrial hypertrophy.

### Selenium

Studies performed in our centre showed increased mutagen sensitivity in *BRCA1* carriers as measured with the bleomycin test. This sensitivity may be normalized with some selenium supplements [55]. Chemoprevention with selenium has been observed to reduce cancer risk in both humans and animals. This question should be answered in *BRCA1* carriers.

## Adnexectomy

Both retrospective and prospective observations of patients with *BRCA1/2* mutations indicate that prophylactic adnexectomy decreases the risk of ovarian/peritoneal cancer to about 5% and breast cancer to 30-40%. Application of adnexectomy together with tamoxifen reduces breast cancer risk to about 10% in *BRCA1* carriers [14]. Therefore, in our centre adnexectomy is recommended to all *BRCA1/2* carriers aged over 35. This surgery is proposed to women from families with HBC-ss, HBOC and HOC but without detected *BRCA1/BRCA2* mutation only if other pathologies of the female genital tract were recorded during control examinations. About 85% of our patients accept this type of prophylaxis [56].

## Mastectomy

The main target of prophylactic mastectomy is reduction of breast cancer risk by removal of tissue at risk. Single cases of breast cancer can develop from the chest wall or from the axillary cave after prophylactic mastectomy. It was noted, however, that only 1% of patients from this group develop breast cancer after prophylactic surgery [57]. It seems reasonable to offer this type of surgery to highly motivated patients with definitively diagnosed high cancer risk, especially where tumoural and mammographically dense breast glands are observed which make early diagnosis extremely difficult. At present, mastectomies with immediate reconstruction are performed most frequently. This procedure ensures a good cosmetic effect [58].

## Surveillance

Surveillance in patients with HBC-ss, HBOC, HOC, as well as in *BRCA1/BRCA2* carriers is shown in Table 4. This scheme is individualized for particular patients with respect to age when particular examinations should begin. In some families where breast cancer was diagnosed before the age of 25 or ovarian cancer before the age of 35 surveillance should begin 5 years earlier than the age of diagnosis of cancer in this family. In some cases, in addition to breast and ovary investigations patients receive colonoscopy, gastroscopy or evaluation of PSA level and prostate ultrasound if in family members symptoms from the colon, gastric or urinal tract are observed. However, it should be noted that some control examinations have limited value in detection of early cancers in *BRCA1* carriers. Ovarian cancer in clinical stage I is detected in only 10% of women with a *BRCA1* mutation. On the other

hand, magnetic resonance imaging in diagnosis of early breast cancers is introducing significant progress [28, 59]. This examination allows detection of 77% of breast cancers with diameter smaller than 1 cm and in combination with ultrasound its sensitivity in detection of early breast cancers rises to over 90% in *BRCA1* carriers [59].

## Treatment

Existing data indicate that different rules should be applied or at least considered as an option in treatment of *BRCA1* carriers. They include:

- radical mastectomy instead of lumpectomy followed by radiation therapy, because the risk of local recurrence in the above procedures is 1% and 8%, respectively (Narod SA, data not published);
- tamoxifen use in spite of ER- breast cancer, because of 50% risk reduction of contralateral breast cancer [53, 60];
- adnexectomy not only because of prophylaxis but also because it was noted that 10-year survival is twice as high in patients after this type of treatment (Narod SA, data not published);
- breast cancer chemotherapy based on schemes without taxanes [61]; treatment results based on schemes with cis-platinum are very promising.

## Syndromes associated with genetic changes of moderately increased risk

The essential problem of clinical genetics is increased hereditary predisposition to breast and ovarian cancer in families with negative history of these cancers. Because of the small number of family members in present families, inheritance by the male line and not full

**Table 4.** Scheme of control examinations in families with high breast/ovarian cancer syndromes

| Organ                | Examination             | Age of beginning (years) | Frequency                                   |
|----------------------|-------------------------|--------------------------|---|
| Breast               | self examination        | 20                       | every month                                 |
|                      | medical palpation       | 20-25                    | every 6 months                              |
|                      | USG                     | 25                       | every 6 months (6 months after mammography) |
|                      | MRI                     | 25                       | every 12 months                             |
|                      | mammography             | 35                       | every 12 months                             |
| Female genital tract | transvaginal ultrasound | 30-35                    | every 12 months                             |
|                      | CA 125                  | 30-35                    | every 12 months (6 months after USG)        |



penetrance, the influence of high risk genes like *BRCA1/2* should be taken into consideration also in such families (about 50% of *BRCA1* mutation carriers with breast cancer come from unaffected families [20]). However, a clear majority of cancers in such families are associated with other factors. The influence of multiple environmental factors on cancer risk has already been documented in the past. Recently, it has been shown that over 90% of patients with breast cancer carry constitutional genetic changes predisposing to development of this cancer [62]. In most cases, they are changes of moderately increased risk. In that context we can suppose that unfavourable environmental factors could lead to cancer development only in patients with a particular genetic background. To date the significance of several genetic changes has been documented in the Polish population, which is the cause for different options of clinical management for these patients. It was found that constitutional changes in the genes *CHEK2* (1100delC, IVS2+1G>A, del5395, 1157T), *NBS1* (657del5), *NOD2* (3020insC), *CDKN2A* (A148T), *BRCA2* (5972C/T polymorphism) and *CYP1B1* (homozygous GTC) are associated with increased breast cancer risk in the Polish population [63, 64]. Carrier status of protein truncated mutation in the *CHEK2* gene (1100delC, IVS2+1G>A, del5395) is associated with about 2.2-fold increased breast cancer risk. This risk concerns both young and older patients [63, 64]. Therefore, the control breast examination in this group of patients starts from 25 years of age according to the scheme shown in Table 5. Carriers of mutation *CHEK2* 1157T have increased cancer risk to a smaller degree (1.4-fold higher than that in the general population).

Occurrence of breast cancer at young age is not characteristic for this kind of mutation. However, patients with this mutation demonstrate lobular type of breast cancer much more often [65]. This cancer is difficult to diagnose using mammography; therefore in this group of patients magnetic resonance imaging (MRI) is recommended from 40 years of age. Mutation 657del5 in the *NBS1* gene is associated with about 3.5-fold increased risk of breast cancer and this increase is the strongest for patients below 40 years old [66] and with positive cancer family history [67]. Mutation 3020insC in the *NOD2* gene is associated with breast cancer at young age (OR=1.9). Characteristic for this mutation is ductal breast cancer with a DCIS component [68]. This kind of cancer is more often accompanied by multiple calcifications; therefore mammography can be useful in prophylaxis of patients with mutations in the *NOD2* gene. Polymorphism 5972C/T in the *BRCA2* gene is also associated with increased risk of breast cancer before 40 years of age (OR=1.4). The risk of cancer development is higher in homozygotes (OR=4.8). This effect is observed at both young and older age [69]. Increased risk is also observed in carriers of *CDKN2A* A148T (OR=1.5) and *CYP1B1* (homozygote GTC) (OR=1.5). In these cases an increased cancer risk at young age is observed. Medical care for patients with genetic changes *NBS1* (657del5), *NOD2* (3020insC), *BRCA2* (5972C/T), *CDKN2A* (A148T), and *CYP1B1* (homozygote GTC) begins at 25 years. Studies on the group of patients with a family history of ovarian cancer allowed characteristic clinical features of ovarian cancers without constitutional mutations in genes *BRCA1* and *BRCA2* to be

**Table 5.** Options of control examinations for carriers of moderate cancer risk gene mutations

| Organ   | Examination       | Age of beginning (years) | Frequency                                       |
|---|-------------------|--------------------------|---|
| <i>CHEK2</i> (1100delC, IVS2+1G>A, del5395), <i>NBS1</i> (657del5), <i>NOD2</i> (3020insC), <i>CDKN2A</i> (A148T) | self examination  | 20                       | every month                                     |
|   | medical palpation | 20-25                    | every 6 months                                  |
|   | USG               | 25                       | every 12 months<br>(6 months after mammography) |
| <i>BRCA2</i> (5972C/T), <i>CYP1B1</i> (homozygote GTC)  | mammography       | 35                       | every 12 months                                 |
| <i>CHEK2</i> (1157T)  | self examination  | 20                       | every month                                     |
|   | medical palpation | 40                       | every 6 months                                  |
|   | USG               | 40                       | every 12 months<br>(6 months after mammography) |
|   | MRI               | 40                       | every 12 months                                 |
|   | mammography       | 40                       | every 12 months                                 |

distinguished. Cancers in this group, unlike cases arising on the basis of *BRCA1* and *BRCA2* mutation, are more often diagnosed in postmenopausal (51-60 years) women and also show lower morphological grading and clinical staging. Analysis of the kind and location of cancers among relatives of examined women showed the increased frequency of ovarian cystadenoma (*cystadenoma ovarii*) [70]. Cystadenomas of the ovary are benign tumours which are able to, in some cases, undergo malignant transformation into borderline malignancy tumours, and sometimes even into cancer (*cystadenocarcinoma*) [71, 72]. For development of this kind of tumours the following constitutional changes can predispose: *NOD2* 3020insC, *CHEK2* I157T, *CYP1B1* 355T/T and *DHCR7* W151X. In the group of "increased risk" there are mainly women at reproductive age ( $\leq 50$  years), who being carriers of at least one of the above-mentioned molecular changes have over twofold increased risk of the development of ovarian borderline malignancy tumours (OR 2.26,  $P=0.0005$ ). Therefore for these women it should be considered to extend the screening options with an additional control examination of transvaginal USG (once a year) from 20-25 years. Early tumour detection and its surgical resection can prevent the development of ovarian cancer. Moreover, in the case of the 355T/T variant *CYP1B1* gene carriers the screening options are extended with an additional control examination for MRI of the breast (once a year) for women aged 30-35 years, on account of almost 3-fold increased risk of the development of cancer of this organ (OR 2.75,  $P=0.03$ ) [73, 74]. The preventive screening is also recommended to first and second degree female relatives of patients with ovarian cystadenoma including:

- control examination by using transvaginal USG (once a year), if in the patient ovarian borderline malignancy tumour and *CHEK2* I157T were detected;
- control breast examination using MRI (once a year) in the case of female relatives of patients with the 355T/T variant of the *CYP1B1* gene and with benign ovarian tumour.

Studies on genetic predisposition to breast cancer or ovarian cystadenoma indicate the existence of multigenetic relations causing high risk of cancer development. It will probably require many years of analysis to discover them.

## Summary

Around 14 000 women develop breast or ovarian cancer in Poland every year. Advances in clinical genetics of cancers allow a significant number of these cancers to be prevented. Additionally, patients of known

genetic background may be more effectively diagnosed and treated due to the application of special, non-standard systems of control examinations and treatment.

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